AMENDMENTS TO THE DRAWINGS

Please replace drawing Figures 1-12, filed December 8, 2003, with the enclosed replacement Figures 1-12.

REMARKS

Claims 1-17 are pending in this application. Independent claims 1 and 9 have been amended to clarify that biomolecules on the microarray are synthesized "by spatially directed synthesis." The synthesis of mircoarrays by spatially directed synthesis is described in detail in the specification. For example, spatially directed oligonucleotide and polynucleotide syntheses are described at page 8, line 13 to page 10, line 23 of the specification. The spatially directed synthesis of other types of molecules is described at page 10, line 24 to page 11, line 5 of the specification. Claim 5 has been amended to delete the redundant term "plurality of" before "biomolecules." Claim 6 has been amended to replace "5 micron" with "5 microns." Accordingly, no new matter is added.

Drawing Objections

A set of formal drawings is submitted herewith, having a better image quality than those filed on December 8, 2003. The replacement drawings more clearly identify the features described in the specification and also address the corrections noted in the Office Action for Figures 2-4.

Reconsideration and withdrawal of the drawing objections are respectfully requested.

Specification Objections

The Office Action requests that the claims be listed in the specification on a separate page. The specification was filed, however, with the claims beginning separately on page 22. The Examples section ends on page 21. The abstract is on a separate page 24. Applicants will

be happy to re-submit these specification pages if the U.S. Patent Office copy is somehow different.

Reconsideration and withdrawal of the specification objections are respectfully requested.

The Rejection of Claim 12 Under 35 U.S.C. § 112, ¶ 2

Claim 12 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the term "heavy." Although "heavy" is a relative term in isolation, it has a definite meaning within the context of the specification and particularly claim 12. Claim 12 recites a "biomolecule target [that] is labeled with a heavy atom." Claim 12 also depends from claim 9 and therefore incorporates the recitation of "scanning . . . using a scanning electron microscope."

One of ordinary skill would be well aware of which heavy atoms could be used for labeling biomolecules in scanning electron microscopy (SEM). In particular, heavy atom labels scatter electrons to enhance the detection of target oligonucleotides using SEM. See page 16, lines 15-16. Heavy atoms are clearly distinguishable using SEM, based on their mass (or atomic number) difference relative to carbon in the biological material. See page 32, last paragraph—page 33, first paragraph of Hermann *et al.*, *Histochem. Cell Biol.* (1996) 106:31-39, already of record. Calcium (and higher atomic number) atoms are considered "heavy" for purposes of labeling and detection in SEM. See the abstract of Risnes *et al.*, *Scand. J. Dent. Res.* (1981) 89(3):205-12 (enclosed). The term "heavy atom" thus has a well recognized and accepted meaning in the art of scanning electron microscopy. The term is not indefinite, as used in claim 12.

Reconsideration and withdrawal of the rejection is respectfully requested.

The Rejections of Claims 1, 2, 4-6, and 8 Under 35 U.S.C. § 102(b)

Claims 1, 2, and 8 are rejected as being anticipated by Takahagi *et al.*, *Jpn. J. Appl. Phys.* (2001) 40: L521-23 ("Takahagi"). Claims 1 and 8 are rejected as being anticipated by Hermann *et al.*, *Histochem. Cell Biol.* (1996) 106:31-39 ("Hermann"). Claims 1, 4-6, and 8 are rejected as being anticipated by Walt *et al.*, U.S. Patent No. 6,210,910 ("Walt"). Applicants respectfully traverse these rejections.

To anticipate a claim, a prior art reference must disclose every element of the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 58 U.S.P.Q.2d 1286, 1291 (Fed. Cir. 2001) (emphasis added). Amended independent claim 1 is (and dependent claims 2, 4-6, and 8 are) directed to a method of detecting biomolecules on a microarray. The method comprises, *inter alia*, "synthesizing said biomolecules on a microarray by spatially directed synthesis." Nowhere is this recited element (or step) disclosed or even suggested in Takahagi, Hermann, or Walt. For at least this reason, the applied references do not anticipate claims 1, 2, 4-6, or 8.

Takahagi teaches the construction of three-dimensional nanoparticle networks, using DNA hybridization to link colloidal gold nanoparticles. In particular, these networks are constructed by covalently bonding 9 nm gold nanoparticles to an oligonucleotide sequence, similarly bonding 20 nm gold nanoparticles to a complementary oligonucleotide sequence, and then hybridizing the sequences in a combined solution under suitable hybridization conditions. See page L521, column 2, 1st paragraph. Consistent with this description, Fig. 1 (see page L522) clearly shows the synthesis occurring, not on a microarray, but in a container of combined reactant solutions. Takahagi therefore does not synthesize biomolecules on a microarray, as claimed.

Hermann teaches the use of gold labeling in SEM. Hermann particularly describes the use of colloidal gold that is directly or indirectly bound to an antibody having affinity for an antigen at the surface of a red blood cell. See Fig. 6. Hermann fails to even mention a microarray. Nonetheless, it is the Office Action's position that

> "It is inherent in the teachings that the red blood cells would have to be placed on a support in order to be scanned with the SEM. The support with a multitude of cells is considered an array."

Office Action at page 6, lines 4-6.

Even accepting *arguendo* that the placement of cells on a support somehow results in a microarray, there is still no teaching or suggestion that biomolecules are synthesized on a microarray, as claimed.

Walt teaches the fabrication of microwells by selective etching of an optical imaging fiber. See Col. 11, lines 33-37. Cells can be dispersed or placed in such microwells, having a diameter which can be adjusted to accommodate most cell types and sizes. See Col. 9, lines 14-26. As discussed above with respect to Takahagi and Hermann, however, nowhere does Walt describe the synthesis of biomolecules on a microarray, as recited in claim 1.

To further clarify the deficiencies in the teachings of the applied references relative to the invention of claim 1, Applicants have amended this claim recite that biomolecules are synthesized by spatially directed synthesis. Applicants teach spatially directed synthesis of biomolecules such as oligonucleotides in detail. For example, see page 8, line 13 to page 11, line 5 of the specification. In particular, spatially directed synthesis refers to methods of directing the synthesis of biomolecules to specific locations on a substrate (*e.g.*, by light-directed oligonucleotide synthesis). See page 8, lines 13-16 of the specification. Such spatially directed synthesis methods generally involve generating active sites (*e.g.*, by removing protective groups)

and coupling these sites to synthesize larger molecules on the substrate. See page 8, lines 18-20. Spatially directed synthesis of a microarray therefore requires synthesis on a substrate, where the synthesis must be directed to specific locations on that substrate. Nowhere is spatially directed synthesis taught or even suggested in Takahagi, Hermann, or Walt.

In summary, the applied references all fail to describe or suggest "synthesizing said biomolecules on a microarray by spatially directed synthesis" as recited in independent claim 1. These applied references therefore do not anticipate claim 1. Claims 2, 4-6, and 8 depend from claim 1 and are therefore novel over the applied references for at least the same reasons.

Reconsideration and withdrawal of these rejections is respectfully requested.

The Rejections of Claims 9 and 11-14 Under 35 U.S.C. § 102(b)

Claims 9 and 11-13 are rejected as being anticipated by Takahagi, and claims 9 and 12-14 are rejected as being anticipated by Hermann. Applicants respectfully traverse these rejections.

To anticipate a claim, a prior art reference must disclose every element of the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 58 U.S.P.Q.2d 1286, 1291 (Fed. Cir. 2001). Amended independent claim 9 is (and dependent claims 11-14 are) directed to a method of analyzing interactions between a biomolecule target and a biomolecule probe on a microarray. The method comprises, *inter alia*, "exposing said biomolecule probe on said microarray to a plurality of biomolecule targets under a hybridization condition." Nowhere is this recited element (or step) disclosed or even suggested in Takahagi or Hermann. For at least this reason, these references do not anticipate claims 9 and 11-14.

It is the Office Action's position that the statement in Takahagi "A droplet of the hybridized solution was cast onto a silicon substrate . . ." amounts to a description of a

microarray. See page 4, last full paragraph and also page 5, lines 4-5. The Office Action similarly contends, as discussed above, that the placement of red blood cells on a support likewise constitutes a microarray. See page 6, lines 4-10.

Even accepting *arguendo* this strained nomenclature, there is still no disclosure in either Takahagi or Hermann of exposing a biomolecule probe on these "arrays" to a biomolecule target under hybridization conditions. This is because the biomolecule probes have already been exposed to their biomolecule targets before the "array" is even made (according to the Office Action's definition). That is, the exposure (resulting in hybridization in Takahagi and antibody/antigen bonding in Hermann) is already complete. There is no exposure of a probe to a target "on said microarray" as recited in claim 9.

Moreover, as discussed above with respect to independent claim 1, independent claim 9 has been similarly amended to clarify that the microarray is synthesized by spatially directed synthesis. In particular, spatially directed synthesis refers to methods of directing the synthesis of biomolecules to specific locations on a substrate (*e.g.*, by light-directed oligonucleotide synthesis). See page 8, lines 13-16 of the specification. Such spatially directed synthesis methods generally involve generating active sites (*e.g.*, by removing protective groups) and coupling these sites to synthesize larger molecules on the substrate. See page 8, lines 18-20. Spatially directed synthesis of a microarray therefore requires synthesis on a substrate, where the synthesis must be directed to specific locations on that substrate. None of these characteristics of spatially directed synthesis is described in Takahagi or Hermann. Clearly, in synthesizing a microarray, it is not enough to simply place a sample of solution or blood on a support, as Takahagi and Hermann describe.

The applied references all fail to describe or suggest "exposing said biomolecule probe on said microarray to a plurality of biomolecule targets under a hybridization condition" as recited in independent claim 9. Furthermore, the applied references similarly fail to describe or suggest a microarray synthesized by spatially directed synthesis, as recited in this claim. These applied references therefore do not anticipate rejected claim 9. Claims 11-14 depend from claim 9 and are therefore novel over the applied references for at least the same reasons.

Reconsideration and withdrawal of these rejections is respectfully requested.

The Rejections of Claims 1-11 Under 35 U.S.C. § 103

Claims 1-11 have been rejected under 35 U.S.C. § 103, as being obvious over McGall *et al.*, U.S. Patent No. 5,843,655 ("McGall"), Takahagi, and McMullan, 51st Annual Meeting of the Microscopy Society of America (August 1993) (McMullan). Applicants respectfully traverse these rejections.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added). Claims 1-11 are directed to methods comprising, *inter alia*, "scanning said microarray with a scanning electron microscope." None of the references McGall, Takahagi, or McMullan teaches or suggests this claimed feature. The legal standard for a *prima facie* case of obviousness is therefore not met.

The Office Action acknowledges that McGall "does not teach using SEM to detect changes in microarrays nor the resolution size of commercially produced SEM's." In fact, McGall makes no mention of SEM whatsoever. Moreover, for the detailed reasons given previously with respect to the anticipation rejections, Takahagi fails to describe or suggest a microarray synthesized by spatially directed synthesis. As a consequence, Takahagi likewise

fails to teach or suggest the *analysis* of such a microarray. Takahagi therefore lacks the disclosure or suggestion of the claimed step, "scanning said microarray with a scanning electron microscope."

Contrary to the Office Action's position (re-iterated in the sentence bridging pages 9-10 and again at page 10, lines 6-7), Takahagi's disclosure of a "droplet of the hybridized solution onto a silicon substrate . . ." does not amount to a description of a microarray. Again, Applicants have further clarified this point by reciting in independent claims 1 and 9 that the microarray is synthesized by spatially directed synthesis, which is clearly not used in the synthesis of Takahagi's "array." Accordingly, scanning the hybridized solution droplet in Takahagi does not constitute scanning a microarray that is synthesized by spatially directed synthesis. At least one claimed step of independent method claims 1 and 9 is therefore neither disclosed nor suggested in the applied references.

In summary, McGall and Takahagi both fail to describe or suggest "scanning said microarray with a scanning electron microscope" as recited in independent claims 1 and 9. This is because McGall is silent regarding the use of a scanning electron microscope. Also, Takahagi fails to teach or suggest a microarray having the meaning in amended claims 1 and 9 (*i.e.*, synthesized by spatially directed synthesis). McMullan does not cure these deficiencies of McGall and Takahagi. These applied references therefore do not render independent claims 1 and 9 obvious. Claims 2-8, 10, and 11 depend from claims 1 and 9 and are therefore patentable over the applied references for at least the same reasons.

Applicants further note that independent claim 9 recites exposing a biomolecule probe on a microarray to targets under a hybridization condition. Takahagi not only fails to describe a microarray, as discussed above, but also fails to provide any suggestion at all to use SEM to

examine hybridization. Takahagi instead confirms DNA hybridization by UV spectroscopy. See page L521, column 2, 3rd paragraph and Fig. 2. SEM is solely "performed to provide visual evidence of the [three-dimensional] construction of the nanostructure." See page L521, column 2, last paragraph and Fig. 3. According to Takahagi, "The internal structure [corresponding to the hybridized DNA "links" between the gold nanoparticles] cannot be observed with SEM." See page L522, column 1.

Reconsideration and withdrawal of these rejections is respectfully requested.

The Rejections of Claims 15-17 Under 35 U.S.C. § 103

Claims 15-17 have been rejected under 35 U.S.C. § 103, as being obvious over the combination of Fodor *et al.*, U.S. Patent No. 5,424,186 ("Fodor"), Seiko Epson Corporation, JP 2001-176941 ("Seiko"), and Ling *et al.*, *Chin. Med. Sci. J.* (2001) 16(1):59-62 ("Ling"). Applicants respectfully traverse these rejections.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added). Independent claim 15 is directed to a method of testing conditions in a microarray manufacturing process. The method comprises, *inter alia*, synthesizing biomolecules on first and second microarrays using manufacturing processes with first and second conditions, respectively. The method first comprises comparing the patterns on these microarrays and selecting a condition for the manufacturing process. None of the applied references teaches or suggests at least the steps of (1) synthesis with first and second conditions and (2) selection of a condition for a manufacturing process. The legal standard for a *prima facie* case of obviousness is therefore not met.

Fodor describes the use of photolithography for the synthesis of polymers on a substrate. In particular, an array of polymers can be synthesized by the exposure of selected regions of the substrate to radiation. The linker molecules on the substrate that have been exposed are rendered reactive with monomers such as nucleotides or peptides. Repetition of the exposure (which can directed at different portions of the substrate using different photomasks) and reaction sequence is used to synthesize particular, known molecules at particular, known locations on the substrate. See col. 2, lines 35-68.

Seiko describes a method for improving automatic defect detectors in semiconductor chip manufacturing. In particular, Seiko recognizes differences in the alignment coordinates of a semiconductor wafer by analyzing the wafer with SEM. See Abstract. The Office Action cites Ling for the proposition that DNA chip technology evolved from computer chip technology in the semiconductor industry[1].

The Office Action contends

> ". . . it would have been *prime* [*sic.*] *facie* obvious to one of ordinary skill at the time the invention was made to improve the method of Fodor et al. by including the combined teachings of Seiko Epson and Ling et al."

Office Action at page 13, lines 1-3.

Even assuming *arguendo* that one of ordinary skill in the art were somehow motivated to combine Fodor, Seiko, and Ling, this combination would not result in the invention of claim 15. This is because Seiko deals solely with detecting defects (or errors), not selecting manufacturing process conditions. By aligning coordinates, Seiko enhances the image obtained of a defective portion of a semiconductor chip. Seiko, however, does not synthesize microarrays with first and second manufacturing process conditions. Nor does Seiko select a condition for a manufacturing

[1] Actually, Ling merely points out that the fabrication techniques (*e.g.*, photolithography) used for computer chips and DNA chips are the same. Ling also recognizes, "DNA chip doesn't process biological information in the same way as computer chip . . ." See page 59, col. 2.

process. Neither Fodor nor Ling cures these deficiencies of Seiko in arriving at the claimed invention.

The combination of Fodor, Seiko, and Ling fails to describe or suggest at least the claimed steps of (1) synthesis of microarrays with first and second conditions and (2) selection of a condition for a manufacturing process, as recited in independent claim 15. These applied references therefore do not render this claim obvious. Claims 16 and 17 depend from claim 15 and are therefore patentable over the applied references for at least the same reasons.

Reconsideration and withdrawal of this rejection are respectfully requested.

The Double Patenting (35 U.S.C. § 101) and Nonstatutory Double Patenting Rejections

Claims 1-13 and 15-17 have been provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-12, 16, and 18-20 of co-pending U.S. Application Serial No. 10/835,434. Claim 14 has been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 17 of the same co-pending U.S. application.

Applicants will consider canceling and/or amending the conflicting claims in co-pending U.S. Application Serial No. 10/835,434 and filing a Terminal Disclaimer when the pending claims are otherwise allowable.

CONCLUSION

In view of the above amendments and remarks, all pending claims of this application are believed to be in condition for allowance. Acknowledgement of the same is respectfully requested.

This response is believed to completely address all of the substantive issues raised in the Office Action dated November 3, 2005.

Respectfully submitted,

Dated: March 16, 2006

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1: Scand J Dent Res. 1981 Jun;89(3):205-12.

Uncoated specimen of human enamel observed in the scanning electron microscope.

Risnes S, Stolen SO.

A 1-mm-thick section of a human premolar was acid etched and observed uncoated in the SEM at accelerating voltages of 3, 5, 10 and 15 kV. Prisms and interprismatic substance were easily distinguishable. Low-voltage operation (3 and 5 kV) gave the best results. Specimen charging was detectable at 5 kV and caused reduced image quality at 10 and 15 kV. Application of silver paste did not reduce charging appreciably. Prolonged observation at high magnification (x 10 000) resulted in contamination of the specimen with consequent charging and reduced resolution. Dental enamel seems to be a material which is well suited when uncoated for observation in the SEM. This may be due both to the high content of the relatively heavy atom calcium, giving good secondary electron emission, and possibly to a certain degree of conductivity caused by diffusible ions.

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